REMARKS

1. Preliminary Remarks

a. Status of the Claims

Claims 17, 20, and 29-32 are pending and under active consideration in this application.

2. Patentability Remarks

a. 35 U.S.C. §§ 101 and 112, first paragraph

On pages 3-14 of the Office Action, the Examiner rejects claims 17, 20, and 29-32 under 35 U.S.C. § 101 because the claimed subject matter allegedly is not supported by either a specific and substantial asserted utility, a credible asserted utility, or a well established utility. The Examiner also rejects these claims under 35 U.S.C. § 112, first paragraph for allegedly lacking utility. In order to satisfy the utility requirement, a specific and substantial utility must either (i) be cited in the specification or (ii) be recognized as well as established in the art, and the utility must be credible. *See In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005) and Revised Interim Utility Guideline Training Materials ("Guidelines").

(1) Specific Utility

A specific utility is a utility that is specific to the particular claimed subject matter, which is in contrast to a general utility that would be applicable to a broad class of inventions. *See Fisher*, 421 F.3d at 1371 and Guidelines. Applicant respectfully submits that the application provides a specific utility for the nucleic acids related to hsa-miR-196b (SEQ ID NO: 354) in accordance with *Fisher* and Guidelines.

Similar to *Fisher*, the current application discloses a large number of nucleic acid sequences. In stark contrast to *Fisher*, however, the instant application provides that each of the disclosed nucleic acids may be used to target and modulate expression of **specific** gene transcripts. Figure Table 4, lines 111,217-111,221 of the application discloses that the claimed miRNA-related sequences specifically target mRNA transcripts of the target gene LHFPL2, as shown below.

GENE NAME	GAM SEQ-ID	TARGET	#BS	TARGET SEQ-ID	TARGET REF-ID	UTR	UTR OFFSET	TAR-BINDING-SITE-SEQ	BINDING-SITE-DRAW (UPPER:GAM;LOWER:TARGET)	SRC	GAM ACC	BS ACC	TAR ACC
GAM7553	354	LHFPL2	1	6663	XP_046054.1	3	2301	GAACCCCAAACC ACTAAAAACTAC CTAAACAC	CCT TG- TAGGTAGTTT GT TTGGG ATCCATCAAA CA AACCC AAT CCA	6	A	c	c

Consequently, the claimed nucleic acids are of a **specific and unique nature** because these nucleic acids regulate the translation of mRNAs from the **specific target gene LHFPL2**. Accordingly, the

asserted utility of the claimed invention is not vague or meaningless, and there is a well-defined public benefit to regulating LHFPL2.

(2) Substantial Utility

To satisfy the "substantial" utility requirement, it must be shown that the asserted use of the claimed invention has a significant and presently available benefit to the public. *See Id.* at 1371 and Guidelines. Applicant respectfully submits that the application provides a substantial utility for the claimed miRNA-related nucleic acids in accordance with *Fisher* and Guidelines.

In *Fisher*, it was admitted that the underlying genes for the ESTs had no known function. *Fisher* argued that this was irrelevant because the seven asserted uses (discussed above) were not related to the function of the underlying genes. Importantly, *Fisher* failed to provide any evidence that any of the claimed ESTs could be used for any of the asserted uses. Consequently, the *Fisher* court concluded that the claimed ESTs were "mere 'objects of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *See Fisher*, 421 F.3d at 1373, *quoting Brenner v. Manson*, 383 U.S. 519 (1966).

In contrast to *Fisher*, the present application discloses that the claimed nucleic acids may be used to bind and regulate mRNA transcripts of LHFPL2. Instant Application, Table 4, lines 111,217-111,221. In addition, LHFPL2 is known to be related to LHFPL, an orthologous gene known to be translocated in chromosomal aberrations in lipomas. *See* Marleen M.R. Petit, *LHFP, a Novel Translocation Partner Gene of* HMGIC *in a Lipoma, Is a Member of a New Family of LHFP-like Genes*, 57(3) Genomics 438, Abstract (1999). LHFPL2 was also known to be expressed in a human immature myeloid cell line KG-1, as well as in a large number of human tissues and cell lines.[1] *See* Takahiro Nagase, *Prediction of the Coding Sequences of Unidentified Human Genes. VI. The Coding Sequences of 80 New Genes (KIAA0201-KIAA0280) Deduced by Analysis of cDNA Clones from Cell Line KG-1 and Brain*, 3 DNA Research 321, 327-328 (1996).

Furthermore, LHFPL2 was later found to be related to the orthologous genes LHFPL3 and LHFPL4, and to the mouse gene *Tmhs* or *hurry-scurry* (*hscy*). *See* Chantal M. Longo-Guess, *A missense mutation in the previously undescribed gene* Tmhs *underlies deafness in hurry-scurry (*hscy*) mice*, 102(22) *PNAS* 7894, 7897-7898 (2005)("Longo-Guess"). Mice that harbor a *hscy/hscy* homozygous loss-of-function genotype cannot hear auditory stimuli up to 110 dB, and exhibit severe degeneration of the organ of Corti, including loss of inner and outer hair cells and decreased spiral ganglia. *See Id.* at

[1] LHFPL2 is also referred to as KIA0206.

7895. Accordingly, modulating LHFPL2, the human homolog of *hscy* and ortholog of LHFPL, using hsa-miR-196b could have a number of presently available benefits to the public. In view of the application providing particular targets of known function for the claimed miRNA-related nucleic acids, Applicant respectfully submits that the specific and substantial utility requirements are satisfied in accordance of *Fisher* and Guidelines.

(3) Credible Utility

On page 8 of the Office Action, the Examiner alleges that Applicant's asserted utility for hsa-miR-196b is not credible. On pages 7 and 8, the Examiner asserts that there is no evidence verifying the expression of any nucleic acid related to hsa-miR-196b, or that any such nucleic acid targets or inhibits a specific gene. Applicant submits herewith experimental evidence that hsa-miR-196b is actually expressed in cells and may regulate the asserted target LHFPL2.

The application as originally filed presented evidence of the actual existence of miR-hsa-196b. Specifically, paragraphs 0199 and 0203 of the specification, and Figure 22 showed that hsa-mir-196b (GAM7553, which is related to SEQ ID NOs: 354 and 48) was specifically detected in a HeLa cell cDNA library. Accordingly, in contrast to the Examiner's assertion that there is no evidence that any of the claimed nucleic exists, Applicant respectfully submits that the application presented the necessary evidence to establish that the claimed nucleic acids exist.

Furthermore, Applicant submits that if human cells do not express the claimed nucleic acids and these nucleic acids do not target LHFPL2, then one of skill would predict that altering hsa-miR-196b activity would have no effect on LHFPL2 expression. On the other hand, if human cells do express the claimed nucleic acids, and these nucleic acids inhibit expression of LHFPL2, as Applicant has asserted, then one of skill would expect that disrupting hsa-miR-196b activity would result in an increase in the level of LHFPL2.

Applicant herewith submits the declaration of Dr. Ayelet Chajut under 37 C.F.R. § 1.132 (the "Chajut Declaration"), which presents the methods and results of experiments that Dr. Chajut supervised and conducted in order to test this hypothesis. The 3'UTR of LHFPL2, as indicated in the portion of Table 4 depicted above, is predicted to contain a binding site for hsa-miR-196b. Thus, binding of this miRNA to its binding site would be predicted to result in a reduction of LHFPL2 mRNA expression levels. Furthermore, transferring the portion of the 3'UTR of LHFPL2 including the miRNA binding site to the 3'UTR of a heterologous gene might also be capable of altering the levels of a corresponding heterologous mRNA. Accordingly, Dr. Chajut's experiments entailed fusing the relevant portion of the 3'UTR of LHFPL2 to a luciferase reporter gene, and then

measuring its effects on a luciferase reporter that lacks the fused 3'UTR, and measuring the effects of an anti-hsa-miR-196b anti-sense oligonucleotide ("ASO") and control ASOs on luciferase levels produced by the luciferase/LHFPL2 3'UTR fusion reporter. *See* the Chajut Declaration, at item 4.

First, if the 3'UTR of LHFPL2 is capable of mediating a decrease in mRNA levels by hsa-miR-196b, then one would predict that fusing the 3'UTR to the luciferase gene would lead to a reduction in luciferase levels produced from such a construct in comparison to a luciferase gene that is not fused to this 3'UTR. In comparison to SNU423 and Hep3B cells transfected with the control luciferase reporter lacking the LHFPL2 3'UTR, cells transfected with the luciferase/LHFPL2 3'UTR fusion reporter exhibit a reduction in luciferase levels. *See* the Chajut Declaration, at items 5 and 6. This result is consistent with an ability of the 3'UTR of LHFPL2 containing a hsa-miR-196b binding site to mediate a decrease in mRNA levels by the miRNA.

If hsa-miR-196b does effect mRNA levels through the LHFPL2 3'UTR, then the hsa-miR-196b ASO would be expected to increase luciferase levels produced by the luciferase/LHFPL2 3'UTR reporter. In the first of the two assays described in the Chajut Declaration, transfecting the hsa-miR-196b ASO together with the luciferase/LHFPL2 3'UTR fusion reporter into SNU423 cells resulted in an increase in luciferase levels from about 0.50 to nearly 0.75 in comparison to luciferase levels in cells transfected only with the reporter, but no ASO. *See Id.* at item 5. In comparison, transfecting a control ASO directed to let7b resulted in an increase in luciferase/LHFPL2 3'UTR reporter levels to 0.63. *See Id.* Accordingly, the increase in luciferase levels in SNU423 cells transfected with the luciferase reporter as compared to cells transfected with the luciferase reporter together with the hsa-miR-196b ASO is consistent with an ability of hsa-miR-196b to regulate LHFPL2 through the 3'UTR of the LHFPL2 3'UTR.

Similar results were observed for Hep3B cells in the second assay described in the Chajut Declaration. Hep3B cells transfected with the luciferase/LHFPL2 3'UTR reporter together with the hsa-miR-196b ASO in comparison to the reporter with no ASO exhibited an increase of luciferase levels from about 0.85 to about 1.25. *See* the Chajut Declaration, at item 6. Additionally, Hep3B cells transfected with the let7B ASO and the reporter had luciferase levels of about 1. *See Id.* These results in Hep3B cells transfected with the luciferase/LHFPL2 3'UTR reporter plus the hsa-mir-196b ASO to the reporter alone are consistent with an ability of hsa-miR-196b to regulate LHFPL2. Overall, the results of both assays suggest that hsa-miR-196b can decrease LHFPL2 mRNA levels through a miRNA binding site located in the LHFPL2 3'UTR.

Applicant submits that evidence described above shows that nucleic acids related to hsa-miR-196b are expressed in human cells and may regulate the asserted target LHFPL2. In view of the foregoing evidence of specific, substantial, and credible utility for the claimed nucleic acid and variants thereof, Applicant requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 101. Additionally, because the hsa-miR-196b-related nucleic acids are supported by a specific, substantial, and credible utility, Applicant respectfully requests that the Examiner reconsider and withdraw the claim rejections under 35 U.S.C. § 112, first paragraph.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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